March 29, 2005

Richard Henrich
Manager, Corporate Regulatory Affairs
Great Lakes Chemical Corporation (GLCC)
P.O. Box 2200
West Lafayette, IN 47996

Dear Mr. Henrich:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 4,5,6,7-Tetrabromo-1,3-isobenzofurandione, posted on the ChemRTK HPV Challenge Program Web site on March 4, 2004. I commend Great Lakes Chemical Corporation and Albermarle Corporation for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Great Lakes and Albermarle advise the Agency, within 60 days of this posting on the Web site, of any modifications to the submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Acting Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
4,5,6,7-Tetrabromo-1,3-isobenzofurandione

Summary of EPA Comments

The sponsors, Great Lakes Chemical Corporation and Albemarle Corporation, submitted a test plan and robust summaries to EPA for 4,5,6,7-tetrabromo-1,3-isobenzofurandione (tetrabromophthalic anhydride, CAS No. 632-79-1) on January 12, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on March 4, 2004. The sponsors submitted a revised test plan and revised robust summaries on February 4, 2004 which were posted on May 18, 2004.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The data submitted for melting point, boiling point, and vapor pressure are adequate for the purposes of the HPV Challenge Program, but robust summaries for boiling point and vapor pressure are missing. The proposed testing for octanol/water partition coefficient and water solubility should await the outcome of stability in water testing.

2. Environmental Fate. The data provided for photodegradation are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured data for stability in water and biodegradation. In addition, the submitter needs to add robust summaries for indirect photolysis and fugacity for data provided in the test plan table.

3. Health Effects. Adequate data are available for the acute and repeated-dose toxicity endpoints for the purposes of the HPV Challenge Program. EPA reserves judgement on the gene mutation and developmental toxicity endpoints pending receipt of additional information. The reproductive toxicity endpoint has not been adequately addressed and thus a combined reproduction/developmental toxicity screening test is needed. EPA agrees with the submitter that an *in vitro* chromosomal aberration assay is needed to address this endpoint. The submitter needs to address deficiencies in the robust summaries.

4. Ecological Effects. EPA reserves judgement on ecological effects testing needs pending receipt of the results of the water stability test and the critical information missing from the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the 4,5,6,7-Tetrabromo-1,3-isobenzofurandione
Challenge Submission

Test Plan

Several studies were submitted for Firemaster PHT-4, FM PHT4 (micronized), and pyrolysis products of HIPS Resin/Sb_2O_3. The submitter needs to state in the test plan and IUCLID Data set whether these are synonyms for the sponsored chemical. Information is also needed on the composition/purity of the tested materials.

Physicochemical Properties (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The data for melting point, boiling point, and vapor pressure are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide robust summaries for boiling point and vapor pressure studies. The submitter's proposals to measure the octanol/water partition coefficient and the

water solubility may not be practical because of the potentially rapid reaction with water. Determination of the stability in water (see below) will help assess whether it is practical to measure these endpoints.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide robust summaries for indirect photolysis and fugacity with input values used in the model estimation.

Stability in water. EPA disagrees with the submitter's view that stability in water testing is unnecessary because "a very minimal amount of this substance is expected to partition to the water column." In the Biodegradation section of the test plan, the submitter indicates that this chemical was rapidly hydrolyzed, and under the conditions of the photodegradation test, it is said to be rapidly hydrolyzed with a half life of <5 min. The Stability in Soil robust summary also cites rapid hydrolysis (no rate data). This potentially useful information cannot be evaluated because the submitter did not provide details of the studies in a robust summary. The submitter needs to provide more data that support a specific hydrolysis rate or provide measured stability in water data for this chemical following OECD TG 111. Clarification of the hydrolysis behavior is essential for design and interpretation of ecotoxicity testing.

Biodegradation. The stability in soil data provided in the test plan are not adequate because such data cannot substitute for a biodegradation study. Depending on results from the stability in water study, the submitter needs to provide measured ready biodegradation data on either the sponsored chemical (if the rate of hydrolysis is slow compared to the biodegradation test period) or its hydrolysis product, tetrabromophthalic acid (if the rate of hydrolysis is rapid), following OECD TG 301.

The fugacity discussion included in this section does not belong under Biodegradation. Several fate-related sections of the test plan are misnumbered.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The data submitted for the acute and repeated-dose toxicity endpoints are adequate for the purposes of the HPV Challenge Program. EPA reserves judgement on adequacy of gene mutation and developmental toxicity endpoints pending receipt of additional information. The reproductive toxicity endpoint has not been adequately addressed. EPA agrees with the submitter that an *in vitro* chromosomal aberration assay is needed to address this endpoint. In addition, the submitter needs to address deficiencies in the robust summaries.

Genetic toxicity: Gene mutations. The data submitted for gene mutation lack essential information that is needed for a data adequacy review. The submitter needs to revise the gene mutation robust summaries with additional information from the original studies.

Reproductive toxicity. No studies were submitted. This endpoint can be addressed by documentation of the evaluation of reproductive organs in a 90-day repeated-dose toxicity study and the availability of an adequate developmental toxicity study. The submitter's plan to use reproductive organ evaluations from the 21- or 28-day repeated-dose toxicity studies is inappropriate, and in fact no such evaluation is reported in the study summaries. A combined reproductive/developmental toxicity screening test is needed to address this endpoint.

Developmental toxicity. The submitted data for developmental toxicity are from a pilot study that used a very small number of animals and generated limited information. If a definitive study was to follow this study, those data should be submitted. If those data are not available and the deficiencies from the pilot study are not addressed adequately, the endpoint will be addressed by the combined reproduction/ developmental toxicity screening test (OECD TG 421) needed for the reproductive toxicity endpoint.

Ecological Effects (fish, invertebrates, and algae)

EPA reserves judgement on ecological effects testing needs and on the adequacy of existing studies pending receipt of the results of the water stability test and the critical information missing from the robust summaries.

Specific Comments on the Robust Summaries

The submitter needs to review and follow Klimisch et al. 1997 guidance for assigning reliability scores because a number of studies appear to be misclassified. The submitter also needs to provide complete citations in the test plan for references Pettigrew (1992) and Weast and Astle (1979).

Health Effects

Gene mutation. Missing information includes test substance/purity, use and response of positive and negative controls, cytotoxic concentration, number of replicates, source of metabolic activation system, criteria for assessing test results, and test conditions/method details.

Repeated-dose toxicity. Information missing from the 28-day repeated-dose dermal toxicity test in rabbits includes the sex of the test animals (discrepancy between the "Sex" and the "Method" fields), frequency of data collection (for clinical signs, body weight, and food and water intake), whether the application site was covered during the exposure period, the specific hematology, clinical chemistry and urinalysis parameters that were examined, the specific organs that were weighed or examined for gross and microscopic pathology, magnitude of body weight changes, the incidences of compound-related lesions by dose and sex, and statistical methods.

Developmental toxicity. Information missing from the pilot teratology study includes maternal and fetal endpoints that were examined (e.g., litter size, litter weight, and examination of fetal organs and/or tissues), data for maternal and fetal body weight changes, and whether statistical methods were used to analyze the data.

Ecological Effects

Fish and Invertebrates. The summaries did not report the composition/purity of the test material, stability of the test material in water, test vessel volume, method of adding the material to the test vessel, toxicological endpoints monitored in addition to lethality, or statistical methods used to analyze test results. The tested concentrations were not clearly stated. The summary reported use of a solvent control, but did not identify the solvent used or its concentration in the test vessel. The values given for the NOEC and LD_{50} were described as "measured/nominal," but no information was provided on analytical methods or measured concentrations over the course of the study.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.